PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 19154.005	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US04/25508	International filing date *(day/month/year)* 05 August 2004 (05.08.2004)	(Earliest) Priority Date *(day/month/year)* 07 August 2003 (07.08.2003)
Applicant CHIRON CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the Report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☒ **Certain claims were found unsearchable** (See Box No. II)
3. ☒ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figures is to be published with the abstract.

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☒ on paper

   ☒ in electronic form

   c. time of filing/furnishing

   ☒ contained in the international application as filed

   ☒ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-3, 5-8, 10-25 and SEQ ID NO:5

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 48/00
US CL : 514/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/004989 A2 (LILLIE ET AL.) 16 January 2003 (16.01.2003) (see in particular, SEQ ID NO: 465, pg. 2, line 30 - pg. 4, line 8; pg. 8. line 16 - pg. 11, line 6; pg. 26, line 25 - pg. 48, line 30)	1-3, 5-8, 10-25
Y	US 5,733,748 (YU ET AL.) 31 March 1998 (31.03.1998) (see in particular SEQ ID NO: 13, Abstract, col. 3, Fig. 13, col. 4, lines 60-67; col. 16 -col. 22).	1-3, 5-8 and 10-25
Y	US 5,988,148 (BENNETT Et Al.) 7 December 1999 (07.12.1999) (col. 2, line 65- col. 25, line 12)	1-3, 5-6, 10-25
Y	BERTRAND ET AL. comparison of antisense oligonucleotides and siRNAs in cell culture and in vivo. Biochem. Biophys. Res. Comm. 2002 Vol., 296: pp. 1000-1004.	7-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 December 2005 (12.12.2005)	05 JAN 2006
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Jon B. Ashen Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (April 2005)

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups 1-15, claim(s) 1-3, 5-8 and 10-25, drawn to a method of making a medicament using a TFF3 neutralizing agent that is an antisense or RNAi molecule that comprises or overlaps any one of SEQ ID NOs: 5-19.

Groups 16-24, claim(s) 1, 9-25 and 59-74, drawn to drawn to a method of making a medicament using a TFF3 neutralizing agent that is an antibody that recognizes at least one region of TFF3 sequence corresponding to one of SEQ ID NOs: 20-28.

Groups 25-33, claim(s) 26-31, 33 and 75-77, drawn to an assay method for detecting TFF3 expression using a TFF3 neutralizing agent that is an antibody that recognizes at least one region of TFF3 sequence corresponding to one of SEQ ID NOs: 20-28.

Group 34, claim(s) 32 and 34, drawn to a method for assessing progression of cancer in a patient comprising comparing TFF3 expression at first and second time points.

Groups 35-49, claim(s) 38-44, drawn to an antisense molecule that modulates the expression of TFF3 that comprises or overlaps any one of SEQ ID NOs: 5-19.

Groups 50-58, claim(s) 45-58, 88-90 and 92-93, drawn to an isolated TFF3 antibody that recognizes at least one region of any one of SEQ ID NOs: 20-28, cell or hybridoma that produces an isolated TFF3 antibody and a composition comprising an isolated TFF3 antibody.

Groups 59-67, claim(s) 79-80 and 87, drawn to an isolated polypeptide comprising amino acid sequences selected from any one of SEQ ID NOs: 20-28.

Groups 68-76, claim(s) 81, drawn to a method of detecting differential expression of TFF3 using an an isolated TFF3 antibody that recognizes at least one region of any one of SEQ ID NOs: 20-28.

Groups 77-80, claim(s) 82-86, drawn to an isolated epitope bearing fragment of SEQ ID NO: 1-4.

Group 81, claim(s) 91, drawn to a method of making an antibody that binds to and neutralizes TFF3.

The inventions listed as Groups 1-81 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:.

Claim 6 of Group 1, the first claimed invention, specifically claims a method of making a medicament wherein the medicament requires an antisense molecule that comprises or overlaps any one of SEQ ID NOs: 5-19.

This international searching authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

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According to the guidelines in Section (f)(i)(a) of Annex B of the PCT Administrative Instructions, the special technical feature as defined by PCT Rule 13.2 shall be considered to be met when all the alternatives of a Markush-group are of similar nature. For chemical alternatives, such as the claimed polynucleotide sequences, the Markush group shall be regarded as being of similar nature when:
(A) all alternatives have a common property or activity and
(B)(1) a common structure is present, i.e., a significant structure is shared by all of the alternatives or
(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to an art recognized class of compounds in the art to which the invention pertains.

The instant antisense oligonucleotide sequences, are considered to be each separate inventions for the following reasons:

The sequences do not meet the criteria of (A), common property or activity or (B)(2), art recognized class of compounds. Although the antisense sequences of the instant application all target a TFF3 gene, each antisense sequence behaves in a different way in the context of the claimed invention. Each sequence targets a different and specific region of a TFF3 gene and each sequence, absent evidence to the contrary, will modulate the expression of a TFF3 gene to varying degrees (as shown in the instant specification, Figure 3, for example). Each member of the class of antisense oligonucleotides cannot be substituted, one for the other, with the expectation that the same intended result would be achieved.

Further, although the instant antisense oligonucleotide sequences target the same "gene" which is "a TFF3 gene", the sequences do not meet the criteria of (B)(1), as they do not share, one with another, a common core structure. Accordingly, unity of invention between the antisense oligonucleotide sequences claimed in the instant application is lacking and each nucleotide sequence claimed is considered to constitute a special technical feature.

For PCT's: If the polynucleotide sequences of the instant invention are recited in the first claimed invention, Applicants will obtain a search of the first sequence listed in the claim. In the instant case, the first sequence listed in claim 6 is SEQ ID NO: 5. For every other sequence applicants wish to have searched, applicants need to elect the sequence and pay an additional fee.

If the sequences are recited in the second or subsequent claimed invention, Applicants will need to elect the group and pay the fee to obtain a search of the first sequence listed in the claims encompassed by the second or subsequent group. For every other sequence in the second/subsequent group that applicants wish to have searched, applicants need to elect the sequence and pay an additional fee.

The special technical feature of Groups 1-15 is a method of making a medicament using a TFF3 neutralizing agent that is an antisense or RNAi molecule that comprises or overlaps any one of SEQ ID NOs: 5-19.

The special technical feature of Groups 16- 24 is a method of making a medicament using a TFF3 neutralizing agent that is an antibody that recognizes at least one region of TFF3 sequence corresponding to any one of SEQ ID NOs: 20-28.

The special technical feature of Groups 25-33 is an assay method for detecting TFF3 expression using a TFF3 neutralizing agent that is an antibody that recognizes at least one region of TFF3 sequence corresponding to any one of SEQ ID NOs: 20-28.

The special technical feature of Group 34 is a method for assessing progression of cancer in a patient comprising comparing TFF3 expression at first and second time points.

The special technical feature of Groups 35-49 is an antisense molecule that modulates the expression of TFF3 that comprises or overlaps any one of SEQ ID NOs: 5-19.

The special technical feature of Groups 50-58 is an isolated TFF3 antibody that recognizes at least one region of any one of SEQ ID NOs: 20-28, cell or hybridoma that produces an isolated TFF3 antibody and a composition comprising an isolated TFF3 antibody.

The special technical feature of Groups 59-67 is an isolated polypeptide comprising amino acid sequences selected from any one of SEQ ID NOs: 20-28.

The special technical feature of Groups 68-76 is a method of detecting differential expression of TFF3 using an isolated TFF3 antibody that recognizes at least one region of any one of SEQ ID NOs: 20-28.

The special technical feature of Groups 77-80 is an isolated epitope bearing fragment of one of SEQ ID NOs: 1-4.

The special technical feature of Group 81 is a method of making an antibody that binds to and neutralizes TFF3.

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Continuation of B. FIELDS SEARCHED Item 3:
EAST, STN (medline, embase, biosis, caplus)
trefoil factor, TFF3, antisense, antibody (SEQ ID NO: 5)